Title

Lipoprotein subfractions and subclinical vascular health in middle aged women: does menopause status matter?

Journal

Menopause The Journal of The North American Menopause Society, 29(8)

ISSN

1072-3714

Authors

Qi, Meiyuzhen

Chen, Xirun

Krauss, Ronald M

et al.

Publication Date

2022-08-01

DOI

10.1097/gme.0000000000001998

Peer reviewed

HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Menopause. 2022 August 01; 29(8): 911–919. doi:10.1097/GME.0000000000001998.

Lipoprotein subfractions and subclinical vascular health in middle aged women: Does menopause status matter?

Meiyuzhen Qi, MPH[a], **Xirun Chen, MPH**[a], **Ronald M. Krauss, MD**[b], **Karen Matthews, PhD**[a,c], **Imke Janssen, PhD**[d], **Maria M. Brooks, PhD**[a], **Dan McConnell, PhD**[e], **Sybil L. Crawford, PhD**[f], **Samar R. El Khoudary, PhD**[a]

[a]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA;

[b]University of California San Francisco Departments of Pediatrics and Medicine, San Francisco, CA;

[c]University of Pittsburgh School of Medicine, Pittsburgh, PA;

[d]Rush University Department of Preventive Medicine, Chicago, IL;

[e]University of Michigan Department of Epidemiology, Ann Arbor, MI;

[f]University of Massachusetts Medical School Graduate School of Nursing, Worcester, MA

Abstract

Objective: During midlife, women experience changes in lipoprotein profiles and deterioration in vascular health measures. We analyzed the associations of groups of lipoprotein subfractions as determined by principal component analysis (PCA) with subclinical vascular health measures in midlife women, and tested if these associations were modified by menopause status.

Methods: PCA was used to generate principal components (PCs) from 12 lipoprotein subfractions quantified among 545 midlife women. The associations of the identified PCs and concurrent vascular health measures were assessed using linear or logistic regressions among participants with carotid intima-media thickness (cIMT, n=259), coronary artery calcium (CAC, n=249) score, or aortic calcium (AC, n=248) scores.

Results: PCA generated 4 PCs representing groups of 1) small, medium, and large very low-density lipoproteins (VLDL) subclasses – VLDL-PC, 2) very small, small, and medium LDL subclasses – small-medium LDL-PC, 3) large and small high-density lipoproteins (HDL) subclasses and midzone particles – HDL-PC, and 4) large LDL and small intermediate-density lipoproteins (IDL) – large LDL-PC. Small-medium LDL-PC was positively associated with cIMT, CAC, and AC in unadjusted but not in adjusted models. Menopause status modified the positive association of the small-medium LDL-PC with cIMT (interaction p-value=0.02) such that this association was stronger after versus before menopause (p-value=0.01).

Corresponding author: Samar R. El Khoudary, PhD, MPH, FAHA, Associate Professor of Epidemiology, Associate Professor of Clinical and Translational Science Institute, Epidemiology Data Center, 4420 Bayard Street, Suite 600, Pittsburgh, PA, 15260, Phone: 412-624-5543, Fax:412-624-3774, elkhoudarys@edc.pitt.edu.

Supplemental Digital Content:
MENO-D-22-00038 supplemental table

Conclusions: Carotid intimal medial thickening is positively and independently associated with small and medium sized LDL particles after menopause. Monitoring levels of specific lipoprotein fractions may have value in identifying midlife women at risk for developing atherosclerotic vascular disease.

Keywords

midlife women; menopause; principal component analysis; lipoprotein subfractions; subclinical vascular health measures

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among women in the United States.[1] The menopause transition is a stage of cardiovascular risk acceleration when women experience deterioration in vascular health metrics [e.g. increases in carotid intima-media thickness (cIMT), adventitial diameter, and pulse wave velocity],[2–4] increases in plasma levels of low-density lipoprotein-cholesterol (LDL-C),[5,6] and dysfunctionality in high-density lipoproteins (HDL).[7,8]

LDL-C and HDL-C, measures that represent the total plasma cholesterol transported in LDL and HDL particles, do not consistently reflect the contributions of these particles to CVD risk, nor do their physico-chemical and functional heterogeneity.[7–10] For example, in midlife women, increases in HDL-C over the menopause transition could not be directly translated into a stronger cardioprotective effect, possibly reflecting reduction of HDL particle size and cholesterol efflux capacity per HDL particle over the menopause transition.[7] Moreover, there are post-menopausal increases in very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and LDL subclasses[11,12] whose contributions to CVD risk also need to be considered.

The large number and complex interrelationships among lipoprotein subfractions[13] present a challenge for assessing their associations with CVD risk. This can be addressed by application of principal component analysis (PCA), an algorithm that creates linear combinations of optimally-weighted variables, thereby reducing the dimensionality of the data while retaining most of its variation.[14] This approach has enabled assessment of associations of independent groups of lipoprotein subfractions measured using ion mobility with CVD related outcomes.[15,16]

In the present report, we have utilized the method of ion mobility to directly measure concentrations of lipoprotein particle fractions as a function of their diameters[17] in a cohort of women spanning the ages of the menopause transition. We used PCA to generate independent groups of lipoprotein subfractions (Principal Components, PCs) and assessed their associations with subclinical vascular health measures [carotid intima media thickness (cIMT), coronary (CAC) and aortic (AC) artery calcium scores]. In addition, we tested whether these associations vary by menopause stage.

METHODS

Participants

The Study of Women's Health (SWAN) is an ongoing multi-racial/ethnic longitudinal study of the menopause transition across 7 sites in the United States (Boston, MA; Detroit, MI; Davis, CA; Los Angeles, CA; Pittsburgh, PA; Chicago, IL; or Newark, NJ). The enrollment eligibility criteria were 1) having a uterus and at least one intact ovary, 2) having a menstrual period within the past 3 months, 3) not pregnant, and 4) not on hormone therapy in the last 3 months. Between 1996 and 1997, 3302 women aged 42–52 years old from the 7 sites completed the baseline enrollment visit. Since then, 16 follow-up visits were completed at approximately annual intervals with longer intervals in more recent years. The SWAN Heart ancillary study was conducted among 608 women from the Chicago and Pittsburgh sites, which only recruited Black and White women without history of cardiovascular disease. Subclinical measurements of vascular health including cIMT, CAC, and AC scores were obtained at the baseline visit of SWAN Heart, coincident with one of the SWAN parent study visits 4 to 7 (between 2000 and 2003). The SWAN HDL ancillary study measured lipoprotein subfractions among 558 SWAN participants from all 7 sites using stored samples collected over the menopause transition, corresponding to SWAN parent study visits 1, 3–9, and 12 to ensure that each woman had at least 1 measure before and 2 measures around/after the menopause onset.

Women with complete ion mobility measurements on all lipoproteins at the baseline visit of SWAN HDL ancillary study were included in the PCA (n=545). To analyze the associations of lipoprotein-PCs and subclinical measures of vascular health, women who additionally had cIMT (n=259), CAC score (n=249), or AC (n=248) score available from the SWAN Heart ancillary study at the same visit at which ion mobility analysis was performed were included (n=263 who had any of the three vascular health measurements of interest).

Research protocols were approved by the institutional review board at each study site, and all participants provided a written informed consent prior to enrollment.

Study Measures

Lipid and lipoprotein measurements—All blood samples were collected after an overnight fast. Plasma cholesterol and triglycerides were measured by the Hitachi 747–200 clinical analyzer as was HDL-C following precipitation of non-HDL lipoproteins heparin-2M manganese chloride. LDL-C was calculated by the Friedewald equation when triglycerides were <400 mg/dL[18] or set to missing when triglycerides were ≥400 mg/dL.

Particle concentrations of VLDL, IDL, LDL and HDL subfractions were analyzed in specific particle-size intervals by ion mobility, which uniquely allows for direct particle quantification as a function of particle diameter[17] following a procedure to remove other plasma proteins[19]. The ion mobility instrument utilizes an electrospray to create an aerosol of particles, which then pass through a differential mobility analyzer coupled to a particle counter. Particle concentrations (nmol/L) were determined for subfractions defined by the following diameter intervals (nm): VLDL: large (42.40–54.70), medium (33.50–42.39), small (29.60–33.49); IDL: large (25.00–29.59), small (23.33–24.99); LDL: large (22.0–

23.32), medium (21.41–21.99), small (20.82–21.40), very small (18.0–20.81); HDL: large (10.50–14.50); small (7.65–10.49). Additionally, concentration of particles sized between LDL and HDL (14.51–17.9 nm, designated midzone) were assessed[20]. Intraassay variation was reduced by inclusion of two in-house controls and by triplicate analysis of each sample. CV <15% for each measurement was maintained throughout.

Subclinical vascular health measurements—Carotid intima media thickness (cIMT) was assessed using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, MA) equipped with a variable frequency (5–12 MHz) linear array transducer. Four images were obtained for each woman by scanning 2 digitized images at each of the right and left distal common carotid arteries. For each image, the near and far wall cIMT measures were obtained by electronically tracing the lumen-intima interface and media-adventitia interface across a 1-cm segment proximal to the carotid bulb; one measurement was generated for each pixel over the area, for a total of approximately 140 measures for each segment. The average values for these measures were recorded for all 4 locations, with the mean of the average at all 4 locations used in analyses.

CAC and AC scores were measured by electron beam computed tomography (EBCT) with an Imatron c-150 Ultrafast CT scanner (Imatron, South San Francisco, CA). All scans were scored at the University of Pittsburgh with a DICOM workstation and software by AcuImage, Inc (South San Francisco, CA) using the method established by Agatston.[21] If at least 3 contiguous pixels showed >130 Hounsfield units, calcification was considered present. During maximal breath holding with ECG triggering to get a 100-millisecond exposure during the same phase of the cardiac cycle (60% of the R-R interval), 30–40 continuous 3-mm-thick transverse images from the level of the aortic root to the apex of the heart were obtained. The CAC score was the sum of the scores for each of the 4 major epicardial coronary arteries[22], while the AC score was from the whole aortic vessel. All scans from the two sites were analyzed by one blinded physician centrally trained with a standardized protocol.

Study covariates—Self-reported race/ethnicity and date of birth were collected at the SWAN screening interview. The following covariates measured concurrently with the independent and dependent variables were included in our analysis. Age was the difference between date of birth and the interview completion date of each visit. Smokers were participants who currently smoked cigarettes or ever smoked a total of at least 20 packs of cigarettes over the life span or at least one cigarette per day for at least 1 year. Antihypertensive medication was defined as taking blood pressure medication since the last visit. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2), measured after removing participants' shoes. Participants were required to sit quietly for 5 minutes before and refrain from talking during the blood pressure measurement. Systolic blood pressure (SBP) was the average of two continuous blood pressure measures assessed with at least a 2-minute interval. Fasting glucose was measured at Medical Research Laboratory, Lexington, KY, using a hexokinase-coupled reaction (Boehringer Mannheim Diagnostics, Indianapolis, IN); coefficient of variation: 1.6%. Serum insulin level was measured using a solid-phase radioimmunoassay (DPC Coat-A-Count Insulin

RIA; Diagnostic Products, Los Angeles, CA); coefficient of variation: 8%. Homeostasis model assessment insulin resistance (HOMA-IR) index was calculated by using the equation [fasting insulin (μIU/mL) × fasting glucose (mmol/L)]/22.5.[23] Ever use of lipid lowering medications included current or past usage of anti-lipemic Statins and anti-lipemic non Statins. Ever use of hormone therapy was defined as past or current usage of at least one of the following medications: estrogen pills, estrogen by injection or patch, progestin pills, combination of estrogen and progestin, and birth control pills.

Menopause status was characterized based on bleeding status into: 1) premenopausal: bleeding in the past 3 months without menstrual cycle changes during the past year; 2) early perimenopause: bleeding in the past 3 months with some menstrual cycle changes during the past year; 3) late perimenopause: bleeding at least once between 3 to 12 months prior to the current visit; 4) naturally postmenopause: no bleeding in at least 12 months prior to the current visit; 5) postmenopausal by bilateral salpingo oophorectomy (BSO): both ovaries removed prior to natural postmenopause; 6) unknown due to utilization of hormones among pre-perimenopausal women; and 7) unknown due to hysterectomy without BSO prior to natural menopause.

Data Analysis—Correlations among the 12 lipoprotein subfractions measured by ion mobility, as well as LDL-C, triglyceride, and HDL-C, were estimated using Spearman correlation coefficients. PCA was performed on the 12 lipoprotein variables to generate independent combinations of them (PCs) that explains the variance of the data. The criteria to detemine the number of major PCs to retain included visual inspection of a scree plot[24], eigenvalues and the proportion of variance accounted[25], and varimax rotated factor loadings for each PC[26]. The PC value of each retained PC was computed for each woman by summing the products of standardized lipoprotein subfraction concentrations (with means 0 and standard deviation 1) multiplied by their scoring coefficients. The PC values were used as independent variables in subsequent modelling with subclinical vascular health measures as outcomes.

Normality of each continuous variable was examined. We have reported median, 25th, and 75th percentiles for non-normally distributed variables. CAC and AC scores were dichotomized by cutoff points 10 and 100 Agatston score, respectively. Due to the small number of women in some original categories, menopause status was regrouped into 4 categories: pre/early perimenopausal, late perimenopausal, postmenopausal (natural and BSO), and unkown due to hormone therapy use or hysterectomy. We applied linear or logistic regression models, as appropriate, to analyze the associations of the major PC values derived from lipoprotein subfractions and each subclinical measure of vascular health. Model 1 adjusted for age, race/ethnicity, study site, menopause status, SBP, antihypertensive medications, and smoking status. Model 2 additionally adjusted for BMI and HOMA-IR, given obesity and insulin resistance are well-known CVD risk factors associated with lipoprotein and lipid metabolism[27,28]. To assess if lipoprotein PCs were associated with outcomes independent of traditional lipids, HDL-C, LDL-C, and triglycerides were added separately to Model 2. We tested whether menopause status modified the effect of each PCs on each subclinical vascular health measure by adding an interaction term to Model 2. We considered: 1) modeling each PC separately as a function of each vascular health outcome

and 2) modeling all PCs together (in one model) as a function of each vascular health outcome. Both approaches generated similar results, and as a result, we only report results from models that included all PCs together. Since the PC values were generated from the full multi-racial sample of women with lipoprotein subfraction data, we conducted a sensitivity analysis of PCs using lipoprotein subfraction data from Black and White participants who had vascular health measures. We then re-assessed the associations of the newly generated PC values from this subsample with cIMT, CAC score, and AC score as described above. Since use of hormone therapy and lipid lowering medications may impact both lipoprotein subfractions and subclinical vascular health status, we additionally adjusted final models for ever use of hormone therapy and ever use of lipid lowering medications.

Statistical analyses were carried out using SAS software 9.4. All P-values are two sided, and $p<0.05$ was considered to be statistically significant.

RESULTS

Table 1 summarizes characteristics of participants (N=545) with ion mobility measurements, as well as the subset (N=263) with both subclinical vascular health and ion mobility measurements. By study design, the subsample only included White and Black participants compared with the full sample, which additionally included Chinese, Hispanic and Japanese women. This difference may have resulted in higher values for the clinical measures (including triglycerides, LDL-C, BMI, SBP, HOMA-IR, and concentrations of all lipoproteins subfractions) in the subsample as compared with the full sample.

Principal component analysis for lipoprotein subfractions

In the correlation analysis (Table 2), all of the 12 lipoprotein subfractions were positively correlated with each other, with varying magnitudes and levels of statistical significance. HDL-C was inversely correlated with all lipoprotein subfractions, except for large HDL and small IDL. The midzone had stronger correlations with small HDL and large IDL concentrations (ρ=0.79, 0.70) than with very small LDL, and small and medium VLDL concentrations (ρ=0.65, 0.64, 0.61). Small IDL particles were highly correlated with large LDL and small VLDL (ρ=0.79, 0.66). Large LDL was most highly correlated with small and large IDL and small VLDL (ρ=0.79, 0.66 and 0.66).

In the PCA, 4 PCs were extracted from the 12 lipoprotein particle fractions that explained 90% of the cumulative variance in the data (Table 3). The first PC (named thereafter based on the highest loading subfraction for this PC: VLDL-PC), which contributed 59% of the total variance, had high loadings of VLDL in the positive direction and comparatively lower loadings of LDL and HDL subfractions in the negative direction. Very small, small, and medium LDL were strongly loaded on the second PC (small-medium LDL-PC). This PC was also negatively associated with VLDL subfractions with lower scoring coefficients. The third PC (HDL-PC) showed high loadings for HDL particles and the midzone. Large LDL and small IDL contributed more to the fourth PC (large LDL-PC). The PC values from the sensitivity analysis using lipoprotein subfractions from Black and White participants had the same factor loading pattern (data not shown).

Principal components and subclinical vascular health measures

In the unadjusted model (Table 4), the VLDL-PC was positively associated with greater odds of CAC score>10 (p=0.04). The small-medium LDL-PC was positively associated with cIMT (p=0.003), CAC score>10 (p=0.001), and AC score>100 (p=0.005), respectively. The other 2 PCs were not related to any subclinical vascular health metric in unadjusted models. In Model 1, the positive associations of small-medium LDL-PC and all three subclinical vascular health measure did not change, but VLDL-PC was no more significantly associated with CAC score>10. With the adjustment of BMI and HOMA-IR in addition to covariates in Model 1, the small-medium LDL-PC was no longer associated with any of the subclinical vascular health measures, and there was a borderline significant negative association between VLDL-PC and cIMT. Additional adjustment for HDL-C, LDL-C, and triglyceride (Supplemental Table 1) did not change the findings.

Effect modification of menopausal status on associations of PCs and subclinical vascular health measures

After separately adding interaction terms between menopause status and each PC values in Model 2, we found that adjusted associations of VLDL-PC, HDL-PC and large LDL-PC with each vascular health measure were not modified by menopause status (data not shown). A positive association between small-medium LDL-PC and cIMT was detected in post-menopausal women (p<0.01), and a similar effect estimate was observed among late peri-menopausal women, but no association was detected in pre or early peri-menopause (interaction p=0.02) (Figure 1, Table 5). The interaction between menopause stage and small-medium LDL-PC for cIMT was still significant when the model was additionally adjusted for HDL-C or triglycerides (interaction p=0.01) and was not significant when the model was additionally adjusted for LDL-C (Table 5). Sensitivity analyses for associations between PCs derived from Black and White participants and subclinical atherosclerosis measures provided similar results (data not shown). Additionally, further adjustment for ever use of hormone therapy and lipid lowering medications did not change the associations between PCs with subclinical atherosclerosis measures (data not shown).

DISCUSSION

Using ion mobility analysis, lipoproteins were physically separated into 12 subfractions by size among midlife women transitioning through menopause, the turning point of vascular health deterioration. The application of PCA identified 4 independent PCs accounting for 90% of the overall variance among the lipoprotein subfractions. The first PC, which primarily represented a relationship among the VLDL subclasses—small, medium and large—accounted for the greatest percentage of variability in this cohort and showed a weak positive association with CAC across all models. However, the estimators of the association became less precise and lost statistical significance after adjusting for covariates. The second PC represented very small, small and medium LDL subclasses, and was positively associated with all vascular health measures in the unadjusted model but not in models adjusted for traditional CVD risk factors. The third PC loaded highly on large and small HDL as well as the midzone and was not related to any subclinical vascular health measure. The last PC heavily loaded on large LDL and small IDL subclasses, and was not associated

with any vascular health measures. This PC was not reported in previous studies which did not focus on midlife women.[15,16] Menopause status only modified the associations of small-medium LDL-PC with cIMT, such that this association was stronger after menopause than before menopause.

In this study, PCA enabled us to identify a group of lipoprotein subfractions, that if elevated after menopause, could increase women's risk of carotid atherosclerosis. This group included very small, small and medium LDL subclasses. Our findings provided additional understanding of previous work from SWAN linking increases in LDL-C during perimenopause with greater risk of carotid plaque[29] by suggesting that very small, small and medium LDL subclasses may contribute to this association. This finding indicates that the role of small and medium LDL in the process of atherogenesis may depend on changes in hormonal, metabolic, and/or vascular status that accompany menopause. Midlife women experience a decrease in estrogen level over the menopause transition. Estrogen may reduce the amount of LDL particles in plasma and protect LDL from oxidative modification in the arterial wall, the initial step of atherogenesis. [30, 31] In addition, our previous study also reported a negative association between estrogen level and small-medium LDL particles. [32]

In our study, menopause status did not modify the associations of the small-medium LDL-PC with CAC or AC scores. This may be due to the fact that CAC and AC are more advanced pathological stages than cIMT, [33, 34] and thus may not be informative at midlife, especially among this cohort with good overall health. Alternatively, the underlying mechanism of the development of CAC and AC in women may not be directly related to estradiol, the cardinal marker of menopause, as is the case for carotid atherosclerosis. In previous work, we did not find an association between estradiol level and CAC or AC in midlife women, although there was a significant association of estradiol with carotid adventitial diameter in this population.[35]

The significant associations between small-medium LDL-PC with cIMT, CAC score, and AC score were attenuated with the additional adjustment for BMI and HOMA-IR indicating that both obesity and insulin resistance at midlife could be pathways through which small-medium LDL-PC may be related to worse subclinical vascular health measures. Insulin resistance and obesity are risk factors of CVD associated with higher levels of small dense LDL and VLDL.[27,28,36–38] During the menopause transition, women experiences increase in fat mass, decrease in lean mass, and deterioration in metabolic syndrome severity score[39,40], which may impact the lipid and lipoprotein metabolism. Thus, small-medium LDL particles may in part mediate the effects of adiposity and insulin resistance on these vascular measures, and/or the small-medium LDL-PC may be a biomarker for vascular effects of adiposity and insulin resistance beyond those due to atherogenic lipoproteins. Notably, the small-medium LDL-PC in this population of midlife women did not fully encompass the components of the PC containing small/medium LDL reported in a previous population-based cohort, as that PC was also strongly loaded with large HDL in the negative direction.[15] In midlife women, large HDL particles decline[7] and this may explain the weak loading of large HDL subfraction on the small-medium LDL-PC among midlife women.

In our sample, we didn't observe a protective association of HDL-PC with vascular health metrics as reported by others in populations that were not limited to women.[15,16] However, when a previous study stratified their data by gender, they did not find a significant association between a PC heavily loaded on HDL subclasses and CVD events among women similar to our results [15]. The non-significant association between the HDL-PC and subclinical vascular health measures in our study suggests a complex association in midlife women who showed potentially adverse changes in HDL subfractions, lipid content, and cholesterol efflux capacity over the menopause transition, underscoring the compositional and functional heterogeneity among HDL particles in midlife women.[7] It is possible that PCA of lipoprotein particle size subfractions is not the best approach for assessing the complexity of the association of HDL with CVD risk in women.

Our study had several strengths. First, when assessing the association between lipoprotein subfractions and subclinical vascular health metrics, we applied PCA to reduce the number of variables to eliminate over-adjustment or collinearity while taking all lipoprotein subfractions and their inter-correlations into consideration. Second, our sample of midlife women with well documented menopausal status encompasses a population who experience deterioration in cardiovascular health over the menopause transition and become more vulnerable to cardiovascular disease after menopause[4]. The major limitation of our study was the small number of women at each menopausal stage, which may lead to underestimating associations at each stage. Besides, the lack of Hispanic and Asian populations in the current analysis may impact the generalizability of our findings. Due to the cross-sectional observational study design of our current analysis, further research will be needed to fully understand the positive association of very small, small, and medium LDL particles with subclinical vascular health measures among midlife women.

CONCLUSION

Very small, small, and medium LDL particles were positively associated with cIMT mainly after menopause among healthy midlife women. In light of the recent scientific statement of the American Heart Association underscoring the menopause transition as a stage of accelerated cardiovascular risk,[4] monitoring levels of the specific lipoproteins found to be related to vascular measures in this study may help to identify women at heightened risk of atherosclerotic CVD at a stage that enables early intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Clinical Centers: *University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994–2011*; *Massachusetts General Hospital, Boston, MA – Sherri-Ann Burnett-Bowie, PI 2020 – Present; Joel Finkelstein, PI 1999 – 2020*; *Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Imke Janssen, PI 2020 – Present; Howard Kravitz, PI 2009 – 2020*; *Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Elaine Waetjen and Monique Hedderson, PIs 2020 – Present; Ellen Gold, PI 1994 – 2020*; *University of California, Los Angeles – Arun Karlamangla, PI 2020 – Present; Gail Greendale, PI 1994 – 2020*; *Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical*

School, Newark – Gerson Weiss, PI 1994 – 2004; and the *University of Pittsburgh, Pittsburgh, PA – Rebecca Thurston, PI 2020 – Present; Karen Matthews, PI 1994 – 2020*.

NIH Program Office: *National Institute on Aging, Bethesda, MD – Rosaly Correa-de-Araujo 2020 - present; Chhanda Dutta 2016- present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers*.

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

SWAN Repository: *University of Michigan, Ann Arbor – Siobán Harlow 2013 - Present; Dan McConnell 2011 – 2013; MaryFran Sowers 2000 – 2011*.

Coordinating Center: *University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001*.

Steering Committee: Susan Johnson, Current Chair. Chris Gallagher, Former Chair

We thank Sarah A. King and Joseph Orr for the ion mobility measurements, the study staff at each site, and all the women who participated in SWAN.

Sources of funding:

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720) and the SWAN repository (U01AG017719). The Study of Women's Health Across the Nation (SWAN) HDL ancillary study has grant support from National Institute on Aging (NIA) AG058690. SWAN Heart was supported by the National Heart, Lung and Blood Institute (grants HL065581, HL065591). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Financial Disclosures/Conflicts of interest:

Dr. Krauss receives money (paid to the institution) from Quest Diagnostics and receives royalties for a patent on ion mobility methodology. Dr. Brooks receives funding from Cerus Corporation. Dr. Crawford receives funding from the University of Pittsburgh. The other authors have nothing to disclose.

REFERENCES:

1. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999–2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999–2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.
2. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. Menopause. Jan 2013;20(1):8–14. doi:10.1097/gme.0b013e3182611787 [PubMed: 22990755]
3. Samargandy S, Matthews KA, Brooks MM, et al. Arterial Stiffness Accelerates Within 1 Year of the Final Menstrual Period: The SWAN Heart Study. Arteriosclerosis, thrombosis, and vascular biology. 2020;40(4):1001–1008. doi:10.1161/ATVBAHA.119.313622 [PubMed: 31969013]
4. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. Dec 22 2020;142(25):e506–e532. doi:10.1161/cir.0000000000000912 [PubMed: 33251828]
5. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. Dec 15 2009;54(25):2366–73. doi:10.1016/j.jacc.2009.10.009 [PubMed: 20082925]

6. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid Changes During the Menopause Transition in Relation to Age and Weight: The Study of Women's Health Across the Nation. American Journal of Epidemiology. 2009;169(11):1352–1361. doi:10.1093/aje/kwp043 [PubMed: 19357323]
7. El Khoudary SR, Chen X, Nasr A, et al. HDL (High-Density Lipoprotein) Subclasses, Lipid Content, and Function Trajectories Across the Menopause Transition: SWAN-HDL Study. Arterioscler Thromb Vasc Biol. Dec 3 2020:Atvbaha120315355. doi:10.1161/atvbaha.120.315355
8. El Khoudary SR, Ceponiene I, Samargandy S, et al. HDL (High-Density Lipoprotein) Metrics and Atherosclerotic Risk in Women. Arteriosclerosis, thrombosis, and vascular biology. 2018;38(9):2236–2244. doi:10.1161/ATVBAHA.118.311017 [PubMed: 30026268]
9. Krauss RM. All low-density lipoprotein particles are not created equal. Arterioscler Thromb Vasc Biol. May 2014;34(5):959–61. doi:10.1161/atvbaha.114.303458 [PubMed: 24740188]
10. Sacks FM, Liang L, Furtado JD, et al. Protein-Defined Subspecies of HDLs (High-Density Lipoproteins) and Differential Risk of Coronary Heart Disease in 4 Prospective Studies. Arterioscler Thromb Vasc Biol. Nov 2020;40(11):2714–2727. doi:10.1161/atvbaha.120.314609 [PubMed: 32907368]
11. Auro K, Joensuu A, Fischer K, et al. A metabolic view on menopause and ageing. Nature Communications. 2014/08/21 2014;5(1):4708. doi:10.1038/ncomms5708
12. Wang Q, Ferreira DLS, Nelson SM, Sattar N, Ala-Korpela M, Lawlor DA. Metabolic characterization of menopause: cross-sectional and longitudinal evidence. BMC Med. Feb 6 2018;16(1):17. doi:10.1186/s12916-018-1008-8 [PubMed: 29402284]
13. Krauss RM, Williams PT, Lindgren FT, Wood PD. Coordinate changes in levels of human serum low and high density lipoprotein subclasses in healthy men. Arteriosclerosis. Mar–Apr 1988;8(2):155–62. doi:10.1161/01.atv.8.2.155 [PubMed: 3348757]
14. Ringnér M. What is principal component analysis? Nat Biotechnol. Mar 2008;26(3):303–4. doi:10.1038/nbt0308-303 [PubMed: 18327243]
15. Musunuru K, Orho-Melander M, Caulfield MP, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular risk. Arterioscler Thromb Vasc Biol. Nov 2009;29(11):1975–80. doi:10.1161/atvbaha.109.190405 [PubMed: 19729614]
16. Aneni EC, Osondu CU, De La Cruz J, et al. Lipoprotein Sub-Fractions by Ion-Mobility Analysis and Its Association with Subclinical Coronary Atherosclerosis in High-Risk Individuals. J Atheroscler Thromb. Jan 1 2019;26(1):50–63. doi:10.5551/jat.40741 [PubMed: 30224606]
17. Caulfield MP, Li S, Lee G, et al. Direct determination of lipoprotein particle sizes and concentrations by ion mobility analysis. Clin Chem. Aug 2008;54(8):1307–16. doi:10.1373/clinchem.2007.100586 [PubMed: 18515257]
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. Jun 1972;18(6):499–502. [PubMed: 4337382]
19. Mora S, Caulfield MP, Wohlgemuth J, et al. Atherogenic Lipoprotein Subfractions Determined by Ion Mobility and First Cardiovascular Events After Random Allocation to High-Intensity Statin or Placebo. Circulation. 2015;132(23):2220–2229. doi:doi:10.1161/CIRCULATIONAHA.115.016857 [PubMed: 26408274]
20. Athinarayanan SJ, Hallberg SJ, McKenzie AL, et al. Impact of a 2-year trial of nutritional ketosis on indices of cardiovascular disease risk in patients with type 2 diabetes. Cardiovascular Diabetology. 2020/12/08 2020;19(1):208. doi:10.1186/s12933-020-01178-2 [PubMed: 33292205]
21. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. Mar 15 1990;15(4):827–32. doi:10.1016/0735-1097(90)90282-t [PubMed: 2407762]
22. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin Proc. Mar 1999;74(3):243–52. doi:10.4065/74.3.243 [PubMed: 10089993]
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin

concentrations in man. Diabetologia. Jul 1985;28(7):412–9. doi:10.1007/bf00280883 [PubMed: 3899825]

24. Cattell RB. The Scree Test For The Number Of Factors. Multivariate Behavioral Research. 1966/04/01 1966;1(2):245–276. doi:10.1207/s15327906mbr0102_10 [PubMed: 26828106]
25. Kaiser HF. The Application of Electronic Computers to Factor Analysis. Educational and Psychological Measurement. 1960;20(1):141–151. doi:10.1177/001316446002000116
26. Kaiser HF. The varimax criterion for analytic rotation in factor analysis. Psychometrika. 1958/09/01 1958;23(3):187–200. doi:10.1007/BF02289233
27. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care. Jun 2004;27(6):1496–504. doi:10.2337/diacare.27.6.1496 [PubMed: 15161808]
28. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. Nutrients. Apr 12 2013;5(4):1218–40. doi:10.3390/nu5041218 [PubMed: 23584084]
29. Matthews KA, El Khoudary SR, Brooks MM, et al. Lipid Changes Around the Final Menstrual Period Predict Carotid Subclinical Disease in Postmenopausal Women. Stroke. 2017;48(1):70–76. doi:10.1161/STROKEAHA.116.014743 [PubMed: 27909203]
30. Wakatsuki A, Ikenoue N, Sagara Y. Effects of estrogen on susceptibility to oxidation of low-density and high-density lipoprotein in postmenopausal women. Maturitas. Jan 12 1998;28(3):229–34. doi:10.1016/s0378-5122(97)00072-8 [PubMed: 9571598]
31. Linton MF, Yancey PG, Davies SS, et al. The Role of Lipids and Lipoproteins in Atherosclerosis. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext. MDText.com, Inc. Copyright © 2000–2021, MDText.com, Inc.; 2000.
32. El Khoudary SR, Brooks MM, Thurston RC, Matthews KA. Lipoprotein subclasses and endogenous sex hormones in women at midlife. J Lipid Res. Jul 2014;55(7):1498–504. doi:10.1194/jlr.P049064 [PubMed: 24852168]
33. Otsuka F, Kramer MC, Woudstra P, et al. Natural progression of atherosclerosis from pathologic intimal thickening to late fibroatheroma in human coronary arteries: A pathology study. Atherosclerosis. Aug 2015;241(2):772–82. doi:10.1016/j.atherosclerosis.2015.05.011 [PubMed: 26058741]
34. Zaid M, Fujiyoshi A, Kadota A, Abbott RD, Miura K. Coronary Artery Calcium and Carotid Artery Intima Media Thickness and Plaque: Clinical Use in Need of Clarification. Journal of atherosclerosis and thrombosis. 2017;24(3):227–239. doi:10.5551/jat.RV16005 [PubMed: 27904029]
35. El Khoudary SR, Wildman RP, Matthews K, et al. Effect modification of obesity on associations between endogenous steroid sex hormones and arterial calcification in women at midlife. Menopause. Aug 2011;18(8):906–14. doi:10.1097/gme.0b013e3182099dd2 [PubMed: 21471825]
36. Adiels M, Olofsson S-O, Taskinen M-R, Borén J. Overproduction of Very Low–Density Lipoproteins Is the Hallmark of the Dyslipidemia in the Metabolic Syndrome. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28(7):1225–1236. doi:doi:10.1161/ATVBAHA.107.160192 [PubMed: 18565848]
37. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovascular Diabetology. 2018/08/31 2018;17(1):122. doi:10.1186/s12933-018-0762-4 [PubMed: 30170598]
38. Cercato C, Fonseca FA. Cardiovascular risk and obesity. Diabetology & Metabolic Syndrome. 2019/08/28 2019;11(1):74. doi:10.1186/s13098-019-0468-0 [PubMed: 31467596]
39. Gurka MJ, Vishnu A, Santen RJ, DeBoer MD. Progression of Metabolic Syndrome Severity During the Menopausal Transition. Journal of the American Heart Association. 2016;5(8):e003609. doi:doi:10.1161/JAHA.116.003609 [PubMed: 27487829]
40. Greendale GA, Sternfeld B, Huang M, et al. Changes in body composition and weight during the menopause transition. JCI Insight. Mar 7 2019;4(5)doi:10.1172/jci.insight.124865

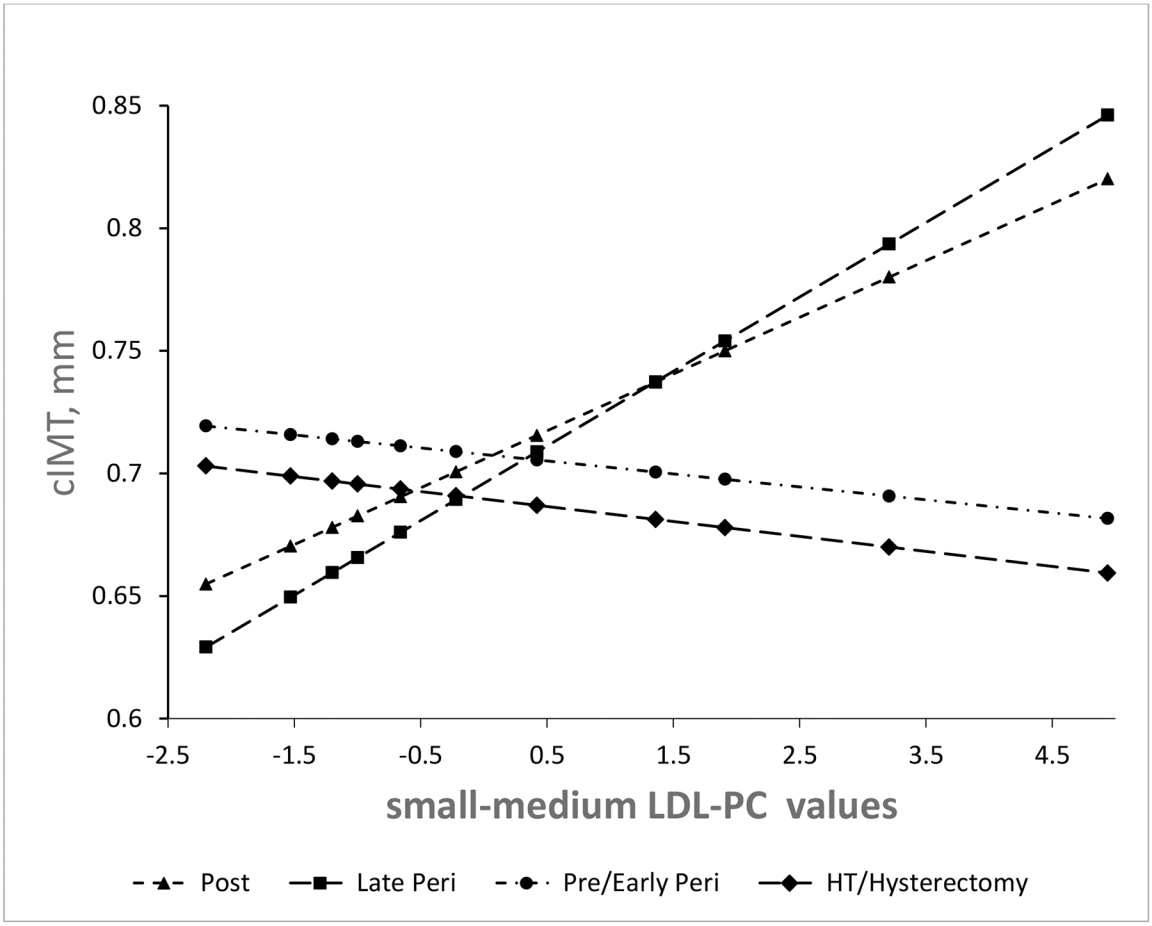

Figure 1.

Plot for interaction between small-medium LDL-PC and menopausal status in model 2[a] for cIMT

There was a significant interaction (interaction p=0.02) between menopause status and small-medium LDL-PC for cIMT in the multivariable model. Compared with pre/early peri- menopausal women (multiple comparison p=0.01), there was a significant positive association (p=0.006) between small-medium LDL-PC and cIMT among postmenopausal women.

[a]Model 2: Adjusted for age, race, site, SBP, menopausal status, antihypertensive medications, smoking status, BMI, and HOMA-IR measured concurrently with lipoprotein subfractions and subclinical vascular health measures. All PCs were included in one model for each subclinical vascular outcome. Predicted cIMT was calculated using means of continuous exposures and reference levels of categorical exposures.

Abbreviations: PC: principal component, LDL, low-density lipoprotein, cIMT: carotid intima-media thickness

Table 1.

Characteristics of study participants at baseline of SWAN HDL ancillary study

Characteristics	Overall sample for PCA (n=545)	Subset with subclinical vascular health measures (n=263)
Age (year), mean (SD)	50.30(2.76)	51.07(2.91)
Race, n(%)		
White	304(55.8%)	174(66.2%)
Black	147(27.0%)	89(33.8%)
Chinese	50(9.2%)	0(0%)
Hispanic	3(0.6%)	0(0%)
Japanese	41(7.5%)	0(0%)
Menopausal Status, n(%)		
Pre-/Early perimenopausal	399(73.2%)	143(54.4%)
Late Peri-menopausal	38(7.0%)	16(6.1%)
Postmenopausal (BSO/Natural)	77(14.1%)	76(28.9%)
Unknow due to HT/hyst	31(5.7%)	28(10.7%)
BMI (kg/m^2), mean (SD)	28.12(6.50)	29.24(6.12)
Smokers, n(%)	55(10.2%)	26(9.9%)
Systolic blood pressure (mmHg), median (Q1, Q3)	112.00(104.00, 125.00)	115.00(106.00, 127.00)
HOMA-IR, median (Q1, Q3)	1.75(1.36, 2.66)	1.89(1.42, 3.06)
Ever users of lipid lowering medication, n(%)	184(33.8%)	122(46.4%)
Ever users of hormone therapy, n(%)	100(18.3%)	93(35.4%)
Triglycerides (mg/dL), median (Q1, Q3)	96.00(73.00, 134.00)	106.00(79.00, 146.00)
LDL-C (mg/dL), mean (SD)	113.24(31.01)	121.31(33.82)
HDL-C (mg/dL), mean (SD)	59.63(14.41)	56.99(13.78)
HDL-L (nmol/L), mean (SD)	15,122.71(3,200.53)	16,767.11(3,449.21)
HDL-S(nmol/L), mean (SD)	5,237.00(1,368.76)	5,610.18(1,530.82)
Midzone (nmol/L), mean (SD)	574.19(155.40)	642.36(175.16)
LDL-VS (nmol/L), mean (SD)	218.25(84.48)	247.30(94.11)
LDL-S (nmol/L), mean (SD)	110.11(68.74)	125.81(80.96)
LDL-M (nmol/L), mean (SD)	140.22(62.23)	161.81(69.87)

Characteristics	Overall sample for PCA (n=545)	Subset with subclinical vascular health measures (n=263)
LDL-L (nmol/L), mean (SD)	364.97(135.19)	428.90(147.08)
IDL-S (nmol/L), mean (SD)	150.88(54.89)	175.13(60.22)
IDL-L (nmol/L), mean (SD)	132.37(42.73)	148.58(49.70)
VLDL-S (nmol/L), mean (SD)	62.91(19.29)	68.68(22.06)
VLDL-M (nmol/L), mean (SD)	47.60(17.34)	52.63(20.22)
VLDL-L (nmol/L), mean (SD)	15.26(7.19)	17.16(8.42)
cIMT (mm), mean (SD)[a]	0.68(0.09)	0.68(0.09)
CAC >0, n (%)[a]	118(47.4%)	118(47.4%)
CAC >10, n (%)[a]	56(22.5%)	56(22.5%)
AC >0, n (%)[a]	172(69.4%)	172(69.4%)
AC >100, n (%)[a]	60(24.2%)	60(24.2%)

[a]Since only 263 women had subclinical vascular health measures, those measures are the same for both samples.

Abbreviation: HDL-S: small HDL, HDL-L: large HDL, LDL-VS: very small LDL, LDL-S: small LDL, LDL-M: medium LDL, LDL-L: large LDL, IDL-S: small IDL, IDL-L: large IDL, VLDL-S: small VLDL, VLDL-M: medium VLDL, VLDL-L: large VLDL, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, cIMT: carotid intima-media thickness, CAC: coronary artery calcium, AC: aortic calcium

Table 2.

Spearman correlation coefficients for lipoprotein subfractions and lipids

Measure	HDL-S	HDL-L	Midzone	LDL-VS	LDL-S	LDL-M	LDL-L	IDL-S	IDL-L	VLDL-S	VLDL-M	VLDL-L	HDL-C	LDL-C	Triglycerides
HDL-S	1	0.58[a]	0.79[a]	0.55[a]	0.41[a]	0.53[a]	0.55[a]	0.51[a]	0.66[a]	0.60[a]	0.60[a]	0.56[a]	−0.001	0.24[a]	0.21[a]
HDL-L	-	1	0.63[a]	0.28[a]	0.06	0.09[b]	0.34[a]	0.56[a]	0.37[a]	0.45[a]	0.29[a]	0.19[a]	0.52[a]	−0.01	−0.08
Midzone	-	-	1	0.65[a]	0.47[a]	0.53[a]	0.49[a]	0.53[a]	0.70[a]	0.64[a]	0.61[a]	0.54[a]	−0.11[b]	0.25[a]	0.20[a]
LDL-VS	-	-	-	1	0.79[a]	0.61[a]	0.25[a]	0.24[a]	0.62[a]	0.44[a]	0.56[a]	0.58[a]	−0.32[a]	0.32[a]	0.59[a]
LDL-S	-	-	-	-	1	0.83[a]	0.19[a]	0.08[b]	0.62[a]	0.37[a]	0.53[a]	0.58[a]	−0.41[a]	0.37[a]	0.45[a]
LDL-M	-	-	-	-	-	1	0.56[a]	0.27[a]	0.76[a]	0.53[a]	0.62[a]	0.60[a]	−0.37[a]	0.51[a]	0.26[a]
LDL-L	-	-	-	-	-	-	1	0.79[a]	0.66[a]	0.66[a]	0.49[a]	0.35[a]	−0.02	0.55[a]	−0.13[b]
IDL-S	-	-	-	-	-	-	-	1	0.56[a]	0.66[a]	0.41[a]	0.25[a]	0.19[a]	0.44[a]	−0.16[a]
IDL-L	-	-	-	-	-	-	-	-	1	0.89[a]	0.90[a]	0.79[a]	−0.23[a]	0.56[a]	0.20[a]
VLDL-S	-	-	-	-	-	-	-	-	-	1	0.90[a]	0.73[a]	−0.03	0.57[a]	0.07
VLDL-M	-	-	-	-	-	-	-	-	-	-	1	0.93[a]	−0.23[a]	0.51[a]	0.30[a]
VLDL-L	-	-	-	-	-	-	-	-	-	-	-	1	−0.30[a]	0.41[a]	0.42[a]
HDL-C	-	-	-	-	-	-	-	-	-	-	-	-	1	−0.22[a]	−0.40[a]
LDL-C	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.24[a]
Triglycerides	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1

a: $p < 0.001$

b : $p < 0.05$

Abbreviation: HDL-S: small HDL, HDL-L: large HDL, LDL-VS: very small LDL, LDL-S: small LDL, LDL-M: medium LDL, LDL-L: large LDL, IDL-S: small IDL, IDL-L: large IDL, VLDL-S: small VLDL, VLDL-M: medium VLDL, VLDL-L: large VLDL

Table 3.

Principal component analysis varimax rotated component matrix results for lipoprotein subfractions

	PCA (n=545)			
Measure	**PC1 VLDL-PC**	**PC2 small-medium LDL-PC**	**PC3 HDL-PC**	**PC4 large LDL-PC**
HDL-S	−0.065	+0.069	**+0.305**	−0.030
HDL-L	−0.083	−0.135	**+0.580**	−0.133
Midzone	−0.081	+0.093	**+0.370**	−0.094
LDL-VS	−0.137	**+0.348**	+0.189	−0.177
LDL-S	−0.157	**+0.466**	−0.072	−0.050
LDL-M	−0.165	**+0.396**	−0.239	+0.253
LDL-L	−0.165	+0.047	−0.198	**+0.608**
IDL-S	−0.128	−0.090	+0.053	**+0.446**
IDL-L	+0.190	+0.022	−0.081	+0.099
VLDL-S	**+0.354**	−0.210	−0.033	+0.073
VLDL-M	**+0.470**	−0.154	−0.070	−0.121
VLDL-L	**+0.482**	−0.109	−0.056	−0.235
% Variance explained	59%	15%	9%	7%

Abbreviation: HDL-S: small HDL, HDL-L: large HDL, LDL-VS: very small LDL, LDL-S: small LDL, LDL-M: medium LDL, LDL-L: large LDL, IDL-S: small IDL, IDL-L: large IDL, VLDL-S: small VLDL, VLDL-M: medium VLDL, VLDL-L: large VLDL

Table 4.

Associations of principal components (modeled together) with each subclinical vascular health measures.

Principal Component	Mean IMT of average (IMT, mm)		CAC score >= 10 (n=58)		AC score >=100 (n=61)	
	Beta (SE)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Unadjusted model						
VLDL-PC	−0.005(0.005)	0.25	**1.30(1.01, 1.67)**	**0.04**	1.25(0.99, 1.60)	0.07
small-medium LDL-PC	**0.015(0.005)**	**0.003**	**1.55(1.20, 2.00)**	**0.001**	**1.43(1.11, 1.83)**	**0.005**
HDL-PC	0.001(0.005)	0.76	1.00(0.76, 1.32)	0.99	1.11(0.86, 1.45)	0.43
large LDL-PC	0.010(0.005)	0.0502	0.87(0.65, 1.14)	0.31	0.99(0.76, 1.29)	0.94
Model 1 [a]						
VLDL-PC	−0.008 (0.005)	0.08	1.29(0.99, 1.68)	0.064	1.17(0.89, 1.55)	0.26
small-medium LDL-PC	**0.001 (0.005)**	**0.015**	**1.51(1.16, 1.98)**	**0.003**	**1.43(1.09, 1.87)**	**0.01**
HDL-PC	−0.005 (0.005)	0.28	0.90(0.66, 1.22)	0.50	1.08(0.80, 1.45)	0.62
large LDL-PC	0.008 (0.005)	0.089	0.84(0.62, 1.12)	0.24	0.99(0.75, 1.31)	0.93
Model 2 [b]						
VLDL-PC	**−0.009(0.004)**	**0.0405**	1.30(0.97, 1.75)	0.08	1.09(0.81, 1.46)	0.56
small-medium LDL-PC	0.006(0.005)	0.20	1.09(0.79, 1.50)	0.61	1.06(0.77, 1.45)	0.72
HDL-PC	−0.008(0.005)	0.11	0.84(0.59, 1.19)	0.32	1.09(0.79, 1.50)	0.62
large LDL-PC	0.008(0.005)	0.11	0.81(0.57, 1.15)	0.23	0.86(0.63, 1.19)	0.37

Abbreviation: PC: principal component, HDL: high-density lipoprotein, LDL: low-density lipoprotein, IDL: intermediate-density lipoprotein, VLDL: very low-density lipoprotein, cIMT: carotid intima-media thickness, CAC: coronary artery calcium, AC: aortic calcium

[a]Model 1: Adjusted for age, race, site, SBP, menopausal status, antihypertensive medications, and smoking status measured concurrently with lipoprotein subfractions and subclinical vascular health measures. All PCs were included in one model for each subclinical vascular outcome.

[b]Model 2: Model 1 + BMI and HOMA-IR

Table 5.

Associations of small-medium LDL-PC and cIMT stratified by menopausal status in model 2[a]

	cIMT, mm								
	Pre/early peri-menopause		Late perimenopause		Postmenopause		HT/Hysterectomy		P value for interaction
	Beta (SE)	p value	Beta (SE)	p value	Beta (SE)	p value	Beta (SE)	p value	
Model 2[a]	−0.005(0.007)	0.42	0.030(0.017)	0.08	**0.023(0.008)** [b]	**0.006**	−0.006(0.019)	0.74	**0.02**
Model 2[a] + HDL-C	−0.007(0.007)	0.29	0.032(0.017)	0.07	**0.028(0.009)** [b]	**0.002**	−0.010(0.019)	0.60	**0.01**
Model 2[a] + triglyceride	−0.006(0.007)	0.40	0.032(0.017)	0.07	**0.029(0.009)** [b]	**0.001**	−0.007(0.019)	0.69	**0.01**
Model 2[a] + LDL-C	−0.006(0.006)	0.39	0.034(0.017)	0.04	0.008(0.010)	0.39	−0.007(0.018)	0.69	0.11

Abbreviation: PC: principal component, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, cIMT: carotid intima-media thickness

[a]Model 2: Adjusted for age, race, site, SBP, menopausal status, antihypertensive medications, smoking status, BMI, and HOMA-IR measured concurrently with lipoprotein subfractions and subclinical vascular health measures. Other PCs were also included in this model with interaction term between menopause status and small-medium LDL-PC.

[b]Significantly different from Pre/early peri-menopause (p-value < 0.05)